REMARKS

RCE

New claims 23–24 constitute a request for continued examination (RCE).

Claims

Claims 1, 2, 4–7 and 9–11 are currently under examination with claims 8 and 12–22 previously withdrawn from consideration due to restriction/election. Claim 3 is cancelled without prejudice or disclaimer. Claims 23–24 are added by this paper.

Claim Amendments

Claim 22 has been amended to recite a method of using the composition(s) of the instant invention, in accordance with conventional US practice.

Support for new claim 23 can be found in, for example, page 20, lines 26–31 of the originally-filed specification and the disclosure contained in the Examples.

New claim 24 reads on the elected species. Support for the claim can be found in the disclosure contained in Examples 1 and 2.

It is respectfully submitted that the claim amendments do not raise new matter.

Restriction/Rejoinder

Instant claims 14–18 are directed to the pharmaceutical composition(s) of the instant invention and read on the elected species. See, page 5 of the Restriction Requirement mailed April 20, 2006 and Applicants' Reply filed July 18, 2006. Insofar as the PTO has agreed to examine the full scope of the genus claim(s), a search and examination of these claims would not pose undue burden on the Examiner. "If search and examination of an entire application can be made without serious burden, the examiner *must* examine it on the merits, even though it includes claims to independent or distinct invention." (Emphasis added). See, MPEP §803. Accordingly, Applicants cordially request a modification of the restriction requirement to include these claims.

Withdrawn claims 22–23 are drawn to a method of using the compositions of claim 1 and recite all the elements of Applicants' composition claims. "If a product claim is found allowable, process claims that depend from or otherwise require all the limitations of the patentable product may be rejoined." See M.P.E.P. § 806.05.

Rejoinder thereof is therefore respectfully requested.

Rejection under 35 U.S.C. §103(a)

The rejection of claims 1-7, and 9-11 under 35 U.S.C. §103(a) as allegedly unpatentable over Thorpe (US 6,703,020) is respectfully traversed.

In maintaining this rejection, the Office Action continues to contend that Thorpe teaches the claimed combination. In page 4, ¶1 of the Office Action, the Office Action states that saturation of the Tie2 receptors by angiopoietin-1 ligand would inhibit binding of the angiopoietin-2 ligand to the receptor, thereby the "combined effect would be inhibition of VEGF [production]." The basis for this rejection is that Thorpe discloses the *possibility* of a simultaneous modulation of both the Tie receptor system as well as VEGF receptor system by angiopoietin-1. This possibility of an *indirect* modulation, the Office Action contends, renders obvious the subject matter of the present claims. Applicants respectfully traverse this contention.

It is submitted that the speculative notion presented in the Office Action fails to provide a legal basis for *prima facie* case of obviousness, which requires that the prior art reference(s) must teach or suggest all the claim limitations. See, MPEP §2143. Since the cited reference does not disclose a composition comprising *compound I* and *compound II*, as claimed herein, Thorpe cannot render obvious the subject matter of Applicants' claims. See, present claim 1. Also the reference is silent as to the activity of these compounds in the modulation of Tie receptor system and VEGF receptor system.

The controlling case law explicitly states that "that which may be inherent is not necessarily known. Obviousness cannot be predicted on hat is unknown." *In re Sporman*, 150 USPQ 449, 452 (CCPA 1966). Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. See, *In re Newell*, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989). Withdrawal of the rejection is respectfully requested.

Even if the speculations rendered in the Office Action were true, Thorpe would still fail to render obvious the subject matter of the present claims in view of the superior tumoricidal effect(s) of the claimed composition over the angiopoietin receptor modulator disclosed in the cited reference. Applicants' specification expressly teaches that the modulation of the two receptor systems unexpectedly results in superior pharmacological effects. See, for example, page 5, lines 23–26 of the instant specification and the experimental data contained in Examples 1 and 2 (Fig. 1 and 2). For example, as summarized in Fig. 1, the average time needed for ectopic melanoma

tumors to reach an end-point size of 250 mm^2 in mice was 24 days for control group (no treatment) and 31 days for mice receiving monotherapy (i.e., angiopoietin inhibitor or VEGF kinase inhibitor). A combination of both angiopoietin inhibitor and VEGF kinase inhibitor increased this time period to 38 days. Corollary studies involving measurement of tumor volume after a given time period (28 days) in control and treated (both monotherapy and combined therapy) mice show similar results. See, the experimental data contained in Fig. 2. In these studies, average tumor volume of ectopic melanoma cells in control group after 28 days was 1000 mm^3, while in mice treated with anti-VEGF antibody (compound I) or sTie2 (compound II) was 450 mm^3 and 600 mm^3, respectively. In mice receiving a combination of compounds I and II, the tumor volume was 250 mm^3.

These studies directly refute the Examiner's contentions. Because if the inhibition of Tie2 receptor also results in the inhibition of VEGF receptor system as allegedly taught by Thorpe (via decreased production of VEGF ligand), then the addition of a VEGF receptor inhibitor should not ameliorate the growth inhibitory effects of the Tie2 antagonist. The data in Figs. 1 and 2 demonstrate otherwise (i.e., a separate pharmacological effect being mediated by the VEGF receptor system). As summarized in the Examples, the combination of two anti-angiogenic principles, which are both considered to be non-cytotoxic, thus results in more than additive tumor growth inhibition. This effect is both novel and unobvious over Thorpe's disclosure.

The rationale for the superior pharmacological effect of the claimed combination is clearly provided in Applicants' instant specification, as originally-filed. For example, the disclosure contained in page 5, lines 26–31 expressly states that the working relationship between compound I and II is that compound I interferes with the VEGF signaling system leading to inhibition of endothelial cell proliferation, migration, and survival in the unsupported premature vessels, whereas compound II interferes with the Tie2 signaling system leading to loosening of endothelial-pericyte and endothelial-smooth muscle cells interactions bringing the vessels in a rather premature status in which the endothelial cells are sensitive to interference with the VEGF-system.

The Examiner is courteously invited to review the disclosure contained page 2, lines 19–31 of Applicants' instant specification and the references cited therein for a background of the pharmacology of the angiopoietin receptor system (the subject matter of Thorpe et al.) It is therein disclosed that Tie2 binds agonistic ligands such as Ang1 which induce rapid activation of Tie receptor tyrosine kinase domain. Other

ligands such as Ang2 bind to Tie2 with similar affinity compared to Ang1 but function as antagonistic ligands blocking Ang1-induced activation of Tie2 receptor (Davis et al., Cell 87, 1161, 1996; Maisonpierre et al., Science 277, 55, 1997). Thus, Tie2 can be either inhibited by inhibition of expression of an agonistic ligand such as Ang1, or by activation of expression of an antagonistic ligand such as Ang2. Similarly, receptor activating ligands (e.g. VEGF-A) as well as antagonistic ligands (e.g. VEGF165b) have been described for the VEGF receptor (Bates & Harper).

Regarding instant claims 10 and 11, it is respectfully submitted that insofar as the cited reference is silent with respect to the combination recited in Applicants' independent claim 1, the subject matter in these claims is also unobvious over the disclosure contained in the art references of record.

Withdrawal of the rejection is respectfully requested.

With respect to the method of treatment claims, enclosed herein are publications by Siemeister et al. ("Inhibition of VEGF receptor kinase." Chapter 22, pp. 339–348, *Angiogenesis in Health and Disease*: Gabor Rubanyi, ed., Marcel Dekker, Inc. New York, NY ISBN: 0-8247-8102-3) and Nagy et al. (Cancer Research, vol. 55, pp. 360–368, 1995), which are directed to the use of VEGF receptor inhibitors in controlling tumor metastasis.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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